IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants:	Anthony E. BOLTON et al.
Title:	INFLAMMATORY CYTOKINE SECRETION INHIBITION
Appl. No.:	10/002,634
Filing Date:	12/5/2001
Examiner:	Michail A. Belyavskyi
Art Unit:	1644
Confirmation No.	1971

BRIEF ON APPEAL

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Sir:

Under the provisions of 37 C.F.R. § 41.37, this Appeal Brief is being filed together with a credit card payment in the amount of $250.00 which is being paid via EFS-Web covering the 37 C.F.R. 41.20(b)(2) appeal fee for a small entity. If this fee is deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 50-0872.

This Appeal Brief is further to the Notice of Appeal filed 25 October 2006 for the above-noted application.[1] A petition requesting a 3 month extension of time accompanies this Brief

[1] The Notice of Appeal inadvertently stated that the appeal was from the Office Action of July 25, 2006 which finally rejected Claims 19-32. However, upon review, this Office Action was a non-final action based on an RCE filed by the Appellants on 1 May 2006 which was filed from a final Office Action dated December 30, 2005. Appellants apologize for any confusion caused by this error.

which is being filed on or before its now current due date of 26 March 2007 (25 March 2007 being a Sunday).

REAL PARTY IN INTEREST

The real party in interest in this application is Vasogen Ireland Ltd., assignee of the entire right, title, and interest in this application by virtue of an assignment from the inventors recorded in the United States Patent and Trademark Office at Reel/Frame 013331/0145 on 25 September 2002. Vasogen Ireland Ltd. is wholly owned by Vasogen Inc.

RELATED APPEALS AND INTERFERENCES

Appellant is unaware of any prior or pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the decision in this application.

STATUS OF CLAIMS

Claims 1-18 were previously canceled and Claims 19-32 are now in this application. These claims are rejected as follows:

Claims 19-32 stand rejected under 35 U.S.C. § 112, first paragraph as containing new matter; Claims 26-32 stand further rejected under 35 U.S.C. § 112, first paragraph as not being enabled

Claims 19-32 stand rejected under 35 U.S.C. § 103(a); and

Claims 19-32 stand rejected under the doctrine of nonstatutory obviousness-type double patenting.

Claims 19-32 are on Appeal.

STATUS OF AMENDMENTS

No amendments have been filed subsequent to the non-final Office Action dated 25 July 2006.[2]

SUMMARY OF CLAIMED SUBJECT MATTER

The invention is drawn to a method of decreasing the expression of one or more of the inflammatory cytokines IFN-γ and IL-6 by cells in a mammalian patient using extracorporeally (i.e., *ex vivo*) stressed autologous blood. *See*, *e.g.*, page 2, lines 14-18, page 3, lines 1-6, and Figures 1 and 2. The invention is also drawn to medical treatment of patients suffering from, prone to, or at risk of contracting, a disorder associated with excessive amounts of one or more of the inflammatory cytokines IFN-γ and IL-6. Page 2, lines 22-26. Such disorders associated with excessive amounts of IFN-γ and/or IL-6 include contact hypersensitivity (CHS). Page 2, lines 25-28. Example 1 describes the treatment of CHS in mice according to the methods of the invention. Page 10, *et seq*.

The blood is stressed extracorporeally by application of two stressors, oxidative conditions and ultraviolet conditions simultaneously (page 4, lines 24-28). The application provides details for stressing the autologous blood using an oxidizing environment (page 5, line 28 to page 6, line 20), and/or ultraviolet radiation (page 6, line 21 to page 7, line 11), and optionally, using the additional stressor of thermal conditions (page 5, lines 7-27). Such conditions are also described in the Example, in the context of treating CHS in mice.

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[2] Appellants note that in their amendment dated 1 May 2006, Claim 19 was amended to include ..."selecting a patient with an excess of inflammatory cytokines, selected from the group consisting of IFN-γ and IL-6..." where the new language introduced has been underlined for ease of reference. However, the claim identifier did not properly identify this claim as currently amended but rather identified it as previously presented. As the Office Action raises a new matter rejection based on this language, Appellants assume that this amendment has been entered. Nevertheless, Appellants apologize for this error.

In addition, Claims 19 and 26 contain inadvertent underlining of commas which in the Claims Appendix have been removed for ease of reading. Upon an indication of allowance of this application, Appellants will amend these claims to remove this underlining.

The identification of a mammalian patient manifesting an excess of inflammatory cytokines, IFN-γ and/or IL-6 is disclosed in the application, for example, at page 3, lines 21-22, at page 8, lines 24-28 and at page 9, line 20 to page 10, line 3.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Six grounds of rejection provide the basis for this Appeal:

1. Claims 19-32 stand rejected under 35 U.S.C. § 112, first paragraph, as containing new matter. The Examiner alleges that "selecting a patient with an excess of inflammatory cytokines, selected from the group of IFN-γ and IL-6" claimed in claim 19 and 26 represent(s) a departure from the specification and the claims as originally filed.

2. Claims 26-32 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking "enablement for a method for treatment or prophylaxis [of] chronic fatigue syndrome in a patient comprising administering to the patient an effective amount of stressed mammalian blood cells..." The Examiner explicitly states:[3]

> "It is the Examiner position that Specification does not reasonably provide enablement for a method for treatment or prophylaxis of any inflammatory disease, including chronic fatigue syndrome in a patient comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation." (emphasis in original).

3. Claims 19-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/07463 in view of Gupta et al., International Journal of Molecular Medicine, 1999, Vol. 3, pages 209-213.[4]

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[3] Office Action of 25 July 2006 at page 3.

[4] Rejections 2-4 were stated in the alternative and collectively presented in paragraph 7 of the Office Action of July 25, 2006. For the sake of completion and ease of reading, each of these rejections will be separately addressed in this Brief.

4. Claims 19-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,980,954 in view of Gupta et al., International Journal of Molecular Medicine, 1999, Vol. 3, pages 209-213.

5. Claims 19-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 00/06703 in view of Gupta et al., International Journal of Molecular Medicine, 1999, Vol. 3, pages 209-213.

6. Claims 19-32 stand rejected under the judicially created doctrine of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 5,980,954 in view of Gupta et al., International Journal of Molecular Medicine, 1999, Vol. 3, pages 209-213.

ARGUMENT

35 U.S.C. § 112, first paragraph – Written Description

Claims 19-32 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to meet the written description requirement. The objective standard for determining compliance with the written description requirement is whether the description clearly allows persons of ordinary skill in the art to recognize that the inventor invented what is claimed. *In re Gosteli*, 873 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The subject matter of the claim need not be described literally (i.e. using the same terms of *in haec verba*) in order for the disclosure to satisfy the description requirement. MPEP § 2163.02.

While the specification may not contain the exact phrase "selecting a patient with an excess of inflammatory cytokines, selected from the group IFN-γ and IL-6," such a selection is clearly described in the specification. For example, at page 2, lines 23-26, the specification explicitly states:

> "...the process of the invention is useful in the medical treatment of patients suffering from, prone to, or at risk of contracting a disorder associated with excessive amounts of one or more of the inflammatory cytokines IFN-γ and IL-6..."

If one of ordinary skill in the art were to medically treat a patient suffering from a disorder associated with excessive amounts of IFN-γ and/or IL-6, the patient by necessity would have to be identified as having excessive amounts of IFN-γ and/or IL-6. Therefore, while the claim limitation objected to by the examiner does not appear *in haec verba* in the specification, identification of patients with excessive amounts of IFN-γ and/or IL-6 is clearly described. Similar support for this limitation can also be found at page 3, lines 1-6, at page 3, line 21 to page 4, line 8 and at page 8, lines 24-28.

Appellants strongly urge withdrawal of this rejection.

35 U.S.C. § 112, first paragraph - Enablement

The examiner rejects claims 26-32 under 35 U.S.C. § 112, first paragraph, because the specification "does not reasonably provide **enablement** for a method for treatment or prophylaxis [sic, *of*] chronic fatigue syndrome in a patient..." (emphasis in original). However, at page 3 of the pending Office Action, the examiner explicitly states that the specification is

> "...enabling for a process of decreasing the expression of one or more of the inflammatory cytokines IFN-γ and IL-6 from cells in mammalian patients comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation..." (emphasis is original)

The standard for determining whether a claim meets the enablement requirement of 35 U.S.C. § 112, first paragraph, is whether one of ordinary skill in the art can practice the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test of enablement is not whether any experimentation is necessary, but rather, whether the experimentation, if necessary, is undue. *In re Angstadt*, 537 F.2d 498,504, 190 USPQ 214, 219 (CCPA 1976). *In re Wands* set forth factors to be considered when

determining whether there is sufficient disclosure to support the claims and whether any required experimentation is "undue." These factors include:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. In rejecting claims 26-32 for lack of enablement, the examiner failed to address any of these factors, except arguably the question of predictability. The MPEP, explicitly instructs that a rejection based on such an analysis is improper.

> It is improper to conclude that a disclosure as not enabling based on an analysis of one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole.

See MPEP § 2164.01(a).

Appellants will address each of the enablement factors in turn below.

Breadth of the claims

Claim 26 is drawn to a method for the treatment or prophylaxis of chronic fatigue syndrome in a mammalian patient characterized by an excessive level of, or excessive sensitivity to, IL-6 cytokines in said patient, which method comprises (1) selecting a patient suffering from or at risk of suffering from chronic fatigue syndrome; (2) withdrawing an aliquot of blood comprising blood cells from said patient; (3) subjecting said blood cells extracorporeally to stress

comprising both oxidative conditions and ultraviolet conditions simultaneously; (4) administering to said patient an effective amount of stressed mammalian blood cells, wherein the level of IL-6 cytokines in said patient is reduced. The claim is limited to treatment or prophylaxis of chronic fatigue syndrome characterized by an excessive level of, or excessive sensitivity to, IL-6 cytokine. Additionally, the protocol of extracorporeally stressing the patient's blood and re-administering that blood to the patient is also limited. The type of stressor is limited to simultaneous application of oxidative and ultraviolet conditions.

Nature of the invention

The *nature* of the claimed invention is that re-administered, extracorporeally-stressed blood provides beneficial effects that transcend a single condition, such as CHS. Because reintroduction of stressed blood produces changes in cytokine levels, the methods of the invention is useful for treating a number of diseases *without additional modification.* This is an important consideration because it means that the need for experimentation is minimal. One skilled in the art need only follow the guidance provided for the treatment of CHS to treat CFS.

State of the prior art

The cited Gupta reference recognizes a correlation between elevated IL-6 levels and chronic fatigue syndrome (CFS). There is not, however, any teaching in this reference as to how to modulate IL-6 levels in patients suffering from CFS.

The Examiner's reliance on the cited Cannon reference (Cannon, et al., J. Clin. Immun., 19(6):414-421 (1999) fails to recognize the teachings of the art as a whole including those found in the cited Gupta reference (Gupta, et al., Int. J. Molec. Med., 3:209-213 (1999) which states at page 209 (in the abstract) that:

> A significant increase in spontaneous, PHA- and LPS-induced IL-6 secretin by both lymphocytes and monocytes was observed in CFS patients during "natural fatigue" as compared to during "rested" state. (emphasis in the original).

Moreover, the Examiner's reliance on Appellants' teaching at page 9 of the specification as characterizing that the art recognized "that [the] etiology of CFS remains unknown" is taken out of context and is, in fact, in error. When read in full context, this teaching reads as:

> Whilst the etiology of CFS remains contentious, there is a general consensus that IL-6 plays a role in CFS, either as a result of abnormal levels of IL-6 in the patient or abnormal sensitivity to IL-6 on part of the patient." (citations omitted)

Nowhere in this cited section of the application, does it spell out that the etiology of CFS is unknown and that statement is only arrived at by extrapolation of the word "contentious" to "unknown".

Level of ordinary skill in the art

Throughout the prosecution of claims 26-32, in their current form and as previously presented as claims 12-18, the Examiner has been silent with regard to the level of ordinary skill in the art. Appellants submit that individuals practicing the claimed invention would have a very high level of skill. The typical practitioner of the claimed invention would have medical training, experience in diagnosis and treatment of chronic fatigue syndrome, and a familiarity with treatments using biological materials, such as extracorporeally stressed blood. Accordingly, a person having ordinary skill in the art pertaining to the present invention would have a least a medical degree, *i.e.* an M.D., and several years of clinical experience.

Level of predictability in art

With regard to the level of predictability in the art, the Office Action states at page 3

> "... since there is no animal model studies and data in the specification to show the effectively of treatment or prophylaxis of chronic fatigue syndrome in a patient comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation it is <u>unpredictable</u> how to correlate a contact hypersensitivity (CHS) test on Balb/c mice and the decrease in the expression levels for cytokines IFN-γ and IL-6 in the lymph tissues of the treated animals with claimed *in vivo* use." (emphasis in the original)

Moreover, the Examiner's reliance on Appellants' teaching at page 9 of the specification as characterizing that the art recognized "that [the] etiology of CFS remains unknown" is taken out of context and is, in fact, in error. When read in full context, this teaching reads as:

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Appellants submit that in coming to a conclusion of unpredictability, the Examiner erred in considering only the disclosure of the specification rather than the particular art at issue. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Therefore it is proper to look at the art itself, rather than solely to the specification. In this regard, predictability must be predicated upon the art providing correlation of overexpression of IL-6 as it relates to CFS. See, e.g., the cited Gupta reference.

Existence of working examples

It is well established that "there is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling.'" *In re Borkowski*, 422 F.2d 904, 909, 164 USPQ 642, 646 (CCPA 1970). Further, as the Federal Circuit stated in a fundamental case on enablement, *In re Vaeck*, "the first paragraph of § 112 requires nothing more than objective enablement ... How such teaching is set forth, either by the use of illustrative examples or broad terminology, is irrelevant." *In re Vaeck*, 947 F.2d 488, 496, n.23, 20 USPQ2d 1438, 1445, n.23 (Fed. Cir. 1991).

The Office Action, at ¶ 5, acknowledges that the specification *is enabling* "for a process of decreasing expression of one or more inflammatory cytokines IFN-γ and IL-6." The specification explicitly identifies CFS as "a disorder associated with excessive amounts of one or more of the inflammatory cytokines IFN-γ and IL-6." Page 2, lines 23-28. The specification further provides a series of references in support of this teaching (*e.g.*, bottom of page 9). Evidence of record admits that there are likely other factors involved in CFS but this admission does not negate the efficacy of the claimed invention – many diseases have complex etiologies.

Since the methods for treating a disease associated with excessive amounts of one or more of the inflammatory cytokines IFN-γ and IL-6 are the same, regardless of the particular

disease, it is immaterial that the example used in the specification is the treatment of CHS rather than CFS. According to the Patent Office's own M.P.E.P. at 2164.02

> "...[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure . . . [t]o make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims."

Here, there is no reason that one could not extrapolate the methods of treatment of CHS to that of CFS because the underlying method for treatment is the same for these two disorders since the underlying causation, *i.e.*, the expression of excessive amounts of one or more of the inflammatory cytokines IFN-γ and IL-6, are, at least in part, the same.

Amount of direction provided by inventor

First, Appellants note that the Examiner has explicitly concluded that the

> "...specification ... [is] enabling for a process of decreasing the expression of one or more of the inflammatory cytokines IFN-γ and from cells in mammalian patients comprising administering to the patient an effective amount of stressed mammalian blood cells wherein said blood cells have been extracorporeally subjected to both oxidative conditions and UV radiation..."[5]

However, the Examiner goes on to conclude that while the specification enables decreasing IL-6 expression, this does not correspond to enabling treatment or prophylaxis of chronic fatigue syndrome. The Examiner specifically cites to the specification and a reference cited therein:

> "... it is well known in the art that excessive sensitivity to IL-6 are almost certainly not the only factor controlling CFS (see [the specification at] page 9, lines 20-25 in particular). In other words Applicants acknowledge that treatment and prophylaxis of CSF [*sic*, CFS] is subject to a number of factors which enter the picture beyond simply reduction in the levels of IL-6 by administering stressed blood cells. Moreover, Cannon et al. (J of Clinical Immunology, 1999, Vol. 19, pages 414-421) teach that there are still some discrepancy in correlation of the levels of IL-6 in serum of CFS patients due to individual variability. Cannon et al., further teach that though abnormalities in cytokine secretion have

[5] Office Action dated 25 July 2006 at page 3.

> been detected in CDF [*sic*, CFS] patient, it is still an open question whether they contribute substantially to the expressions of CFS (see page 420 in particular)."[6]

As disclosed in Gupta et al., *Int'l J Molec Med* 3:209-213 (1999), at page 210 (right column), increased IL-6 levels are specifically correlated with fatigue symptoms in patients suffering from chronic fatigue syndrome.

> "Fig. 1 shows that spontaneous IL-6 secretion by lymphocytes was significantly higher ($P<0.01$) in patients with CFS when 'fatigued' (908±6237 pg/ml) as compared to when 'rested' (310±317 pg/ml). Fig. 2 shows that healthy normal controls tested on two separate occasions did not show any significant different in spontaneous IL-6 production (Run 1: 48 ±32 pg/ml; Run 2: 56±44 pg/ml)."

Thus, one would expect a decrease in IL-6 levels to have a beneficial effect on a CFS patient. Since the Examiner has determined that the specification is enabling for just such a decrease in IL-6 expression, it logically follows that the specification provides adequate support for treating and/or preventing the symptoms of chronic fatigue syndrome.

The Office Action[7] also asserts that there is no animal model for CFS and that it would be unpredictable to how to correlate the data obtained in mice with *in vivo* results. At the outset, Appellants note that experiments in mice are *in vivo* results. The question relevant to the enablement issue must, therefore, be whether the *in vivo* results obtained in treating CHS in mice are applicable to the *in vivo* treatment of CFS in humans. Appellants have already addressed this issue above, in the discussion of "***Existence of working examples***." The remaining question is whether the description of the treatment of mice is enabling for the treatment of humans. If it is not, countless issued U.S. patents should be withdrawn from issue. U.S. Patent law has never required the disclosure of studies in humans to support claims drawn to the treatment of humans.

Quantity of experimentation

The standard for enablement is whether "one reasonably skilled in the art could make or use the invention . . . without undue experimentation." *Hybritech Inc. v. Monoclonal Antibodies,*

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[6] Office Action dated 25 July 2006 at page 4.

[7] Office Action dated 25 July 2006 at page 4.

Inc. 802 F.2d 1367, 1384 (Fed. Cir. 1986). Here, by simply following the guidance provided in the specification with respect to CHS one skilled in the art could apply the invention to CFS. There is minimal *experimentation* necessary.

The Office Action at page 4 (first full paragraph) alleges that the specification is not enabling for methods of prevention/prophylaxis, as opposed to treatment. However, methods of prevention, as well as treatment, are enabled by the specification. The specification states, at the bottom of page 2, that "the invention is useful in the medical treatment of patients suffering from, *prone to, or at risk of contracting* a disorder associated with excessive amounts" of IFN-γ and IL-6 (emphasis added). See also page 9, lines 20-23, of the specification. The methodology for treatment is the same as that for prophylaxis, which is fully disclosed in the specification. Moreover, there would appear to be no basis for distinguishing between *treatment* and *prophylaxis*, in terms of compliance with the enablement requirement.

The rejection appears to add a layer of complexity to the prophylactic use of the invention in stating that "the specification does not provide guidance . . . [for] . . . screening those patients susceptible to any inflammatory disease."[8] To the extent that any screening would be required to practice the invention for prophylaxis, such screening is readily apparent from reading the specification. Such individuals would present with increased levels of the cytokines that the claimed methods are disclosed to reduce. The levels of these cytokines are clearly measurable since they are measured in the Example and are the subject of Figures 1 and 2.

Thus, based on the factors specified in *In re Wands, supra*, prophylaxis/prevention, as well as treatment, of disorders associated with excessive levels of IL-6 and IFN-γ, are enabled by the specification, or by the specification combined with the knowledge of those skilled in the art.

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[8] Page 4, last paragraph of the Office Action.

35 U.S.C. § 103(a) – WO 98/07463 in view of Gupta et al.

Claims 19-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 98/07463 in view of Gupta et al. *Int'l J Molec Med* 3:209-213 (1999). Appellants submit that the examiner has failed to provide a *prima facie* case of obviousness and likely has misidentified the primary reference.

The Office Action dated 25 July 2006 characterized WO 98/07463 as "teach[ing] a method of treating an inflammatory disease including inflammatory bowel disease and rheumatoid arthritis in a mammalian patient [which method] comprises administering to the patient stressed mammalian blood cells (see the entire document, pages 1, 17 and 23 in particular)." However, a review of WO 98/07463 shows that it is drawn to needle assembly with a needle holder, a needle sleeve moveable over the needle holder and an interlocking member engaging the needle sleeve and the needle holder. The application is 21 pages long, making a reference to page 23 improbable. The WO 98/07463 reference contains no allusion to stressed autologous blood, treatment of and disorder, inflammatory or otherwise. The combination of WO 98/07463 with Gupta et al. does not teach or suggest any limitation of present claims.

Appellants urge withdrawal of this rejection.

35 U.S.C. § 103(a) – U.S. Patent No. 5,980,954 in view of Gupta et al.

The Examiner bears the initial burden of presenting and factually supporting a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met:

1. there must be some suggestion or motivation in the references themselves, to modify the reference or combine the reference teachings;

2. there must be a reasonable expectation of success; and

3. the prior art references, when combined, must teach or suggest every element of the claim.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Appellants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Appellants submit that the Examiner has failed to meet at least two of the three basic criteria and, therefore, the rejection must be withdrawn.

(1) One of Ordinary Skill Would Not Be Motivated to Combine the References

The Office Action dated 25 July 2006 characterized U.S. Patent No. 5,980,954 as "teach[ing] a method of treating an inflammatory disease including inflammatory bowel disease and rheumatoid arthritis in a mammalian patient [which method] comprises administering to the patient stressed mammalian blood cells." The Action proceeds to point out that the manner in which the blood is stressed is similar to that disclosed and claimed in the present application. Appellants submit that the Office Action has mischaracterized the disclosure of U.S. Patent No. 5,980,954 ("the '954 Patent").

The '954 Patent discloses method of treating mammalian patients suffering from an autoimmune disease (see column 1, lines 12-16, column 5, lines 21-24, and claim 1) by administering an autovaccine comprising an aliquot of extracorporeally stressed blood, wherein the stressed blood has at least one specified feature. At column 5, lines 31-59, the '954 Patent indicates that the autovaccine acts by altering the ratio of Th1 and Th2 cells. This reference does not indicate that the autovaccine is capable of decreasing expression of an inflammatory cytokine selected from IFN-γ and IL-6. Indeed, the Examiner acknowledges that U.S. Patent No. 5,980,954 does not explicitly teach a method of decreasing expression of one or more inflammatory cytokines selecting from the group of IFN-γ and IL-6, as recited in claims 19-25 or treating or prophylaxis of chronic fatigue syndrome (CFS) as recited in claims 26-32[9].

The Office Action asserts that one or ordinary skill in the art would have been motivated to "apply the teachings of Gupta et al. to those of ... U.S. Patent No. 5,980,954" because

[9] Office Action dated 25 July 2006 at page 6 and July 12, 2005 at page 8.

"overproduction of IL-6 contributed to many inflammatory diseases including patient with chronic fatigue syndrome." In coming to this conclusion, the Office Action ignores that the '954 Patent is drawn to the treatment of autoimmune diseases, not chronic fatigue syndrome or conditions characterized by over-expression or hypersensitivity to IL-6 or IFN-γ. While certain autoimmune disorders may have an inflammatory component, it is a very large leap from recitation of "autoimmune disorder" to chronic fatigue syndrome or any other disease characterized by over-expression of IL-6 or IFN-γ.

While the '954 Patent is entirely silent with regard to chronic fatigue syndrome and/or expression of IFN-γ and IL-6, the Gupta et al. reference narrowly focuses on the specific question of whether there is a correlation between fatigue and expression of IL-6 by monocytes and lymphocytes in CFS patients. Appellants submit that there is no nexus between these two references that would lead one of ordinary skill in the art to combine the teachings. Indeed, the Gupta reference explicitly states in the last sentence of page 212 that

> Because IL-6 is produced by a subset of CD4+ (Th2) and CD8+ (Tc2) cells, the present investigation did not delineate the cellular source of IL-6 abnormality in CFS. Studies are in progress to analyze intracellular cytokines in CD4+ and CD8+ T cell in CFS to define the cellular source (Th1/TC1 and Th2/TC2 cells) of altered cytokine production in CFS. (citations omitted)

Thus, the Gupta et al. reference teaches that one cannot identify the source of the IL-6 within a population of Th1 cells or Th2 cells. Accordingly, there is no motivation to utilize the method of the '954 Patent in conjunction with the disorder, chronic fatigue syndrome, studied by the authors of the Gupta et al. reference.

(2) One of Ordinary Skill Would Have No Expectation of Success

Just as the lack of nexus between the '954 Patent and the Gupta et al. reference would fail to motivate one of ordinary skill in the art to combine the teachings of these references, this individual would have no expectation of success if the method of treating an autoimmune disorder as taught by the '954 Patent were applied to the condition studied by Gupta et al., *i.e.*, chronic fatigue syndrome. Gupta et al. acknowledges a lack of information regarding any bias in

IL-6 production in Th1 and Th2 cell populations. The '954 Patent fails to mention any reference to CFS. As such, there is nothing in either reference, alone or combined, that would form the basis for the skilled artisan to conclude that there could be a reasonable expectation of success in treating CFS.

Because at least two of the three basic criteria for presenting a *prima facie* case of obviousness have not been met, Appellants request withdrawal of the rejection of claims 19-32 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,980,954 in view of Gupta et al.

35 U.S.C. § 103(a) – WO 00/06703 in view of Gupta et al.

As discussed above, the Examiner bears the initial burden of presenting and factually supporting a *prima facie* case of obviousness. Appellants submit that the Examiner has failed to meet at least two of the three basic criteria necessary to make a *prima facie* rejection, and therefore the rejection must be withdrawn.

(1) One of Ordinary Skill Would Not Be Motivated to Combine the References

The Office Action dated 25 July 2006 characterized WO 00/06703 as "teach[ing] a method of treating GVHD in a mammalian patient [which method] comprises administering to the patient stressed mammalian blood cells (see the entire document Abstract in particular ." The Action proceeds to point out that the manner in which the blood is stressed in WO 00/06703 is similar to that disclosed and claimed in the present application. Notably, the disclosure of WO 00/06703 describes administration of allogenic cells[10], *i.e.* cells from another donor, not autologous blood as required by the present invention.

While WO 00/06703 is entirely silent with regard to chronic fatigue syndrome and/or expression of IFN-γ and IL-6, the Gupta et al. reference narrowly focuses on the specific question of whether there is a correlation between fatigue and expression of IL-6 by monocytes and lymphocytes in CFS patients. Appellants submit that neither reference provides a nexus between

[10] See WO 00/06703 at page 3, lines 21-27, and page 4, line 16 to page 7, line 8.

graft versus host disease (GVHD) and chronic fatigue syndrome. Accordingly, the references fail to provide any motivation to combine the disclosure of IL-6 and chronic fatigue syndrome of Gupta et al. with the administration of modified blood as disclosed in WO 00/06703.

(2) The References When Combined Do Not Disclose Every Limitation of the Claims

Even if one were to combine the method of WO 00/06703 with the studies described in Gupta, et al., this combination would not disclose every limitation of the present claims. First, neither reference teaches a method of decreasing expression of IL-6 or IFN-γ (as required by claims 19-25) or a method of treating or preventing chronic fatigue syndrome (as required by claims 26-32). Second, neither reference discloses withdrawing an aliquot of blood from a patient, stressing that blood and re-administering the aliquot to the same patient (as required by claims 19-32). Gupta et al. is silent with regarding to stressed blood. WO 00/06703 described obtaining blood or blood fractions from allogenic donors. For this reason alone, the rejection of claims 19-32 under 35 U.S.C. § 103(a) over WO 00/06703 in view of Gupta et al. should be withdrawn.

(3) One of Ordinary Skill Would Have No Expectation of Success

Just as the lack of nexus between WO 00/6703 and the Gupta et al. reference would fail to motivate one of ordinary skill in the art to combine the teachings of these references, this individual would have no expectation of success if the method of treating graft versus host disease as taught by WO 00/06703 were applied to the condition studied by Gupta et al., *i.e.*, chronic fatigue syndrome. Without some reason to believe that the conditions underlying graft versus host disease are connected with inappropriate expression of or sensitivity to IL-6, one of ordinary skill in the art would have no expectation that a treatment for graft versus host disease would have any effect on chronic fatigue syndrome.

As none of the three basic criteria for presenting a *prima facie* case of obviousness have been met, Appellants request withdrawal of the rejection of claims 19-32 under 35 U.S.C. § 103(a) over WO 00/06703 in view of Gupta et al.

Obviousness-type Double Patenting

The examiner rejects claims 19-32, as being unpatentable over claims 1-12 of U.S. Patent N0. 5,980,954 in view of Gupta et al. Initially, it is noted that an obviousness-type double patenting rejection is analogous to an obviousness rejection under 35 U.S.C. §103 with the exception that the cited patent application, in this case, is not considered prior art. See, e.g., MPEP §804B(1). The test for non-obviousness articulated by the Court of Appeals for the Federal Circuit in *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) requires consideration of at least the following factors: (1) whether there is some suggestion or motivation in the references themselves, to modify the reference or combine the reference teachings; and (2) whether the prior art would also have provided a reasonable expectation of success to such a skilled artisan. As discussed above, one of ordinary skill in the art would not be motivated to combine the teachings of U.S. Patent No. 5,980,954 and Gupta, et al., nor would such a person of ordinary skill in the art have any expectation of success if such a combination were made. Appellants urge withdrawal of this rejection.

SUMMARY

As noted above, Appellant concludes that the rejection of Claims 19-32 under 35 U.S.C. §112, first paragraph, under 35 U.S.C. § 103 and under the nonstatutory doctrine of obviousness-type double patenting is in error. Appellant requests that the Honorable Board of Patent Appeals and Interferences render a similar conclusion.

Respectfully submitted,

Date 3-26-07

By _____

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CLAIMS APPENDIX

Claims 1-18 (Cancelled)

19. A method of decreasing expression of one or more inflammatory cytokines, selected from the group of IFN-γ and IL-6, in a mammalian patient, said method comprising:

selecting a patient with an excess of inflammatory cytokines, selected from the group of IFN-γ and IL-6;

withdrawing an aliquot of blood comprising blood cells from said patient;

subjecting said blood cells extracorporeally to stress comprising both an oxidative condition and an ultraviolet stressor simultaneously;

administering to said patient an effective amount of stressed mammalian blood cells, wherein the expression of one or more inflammatory cytokines in said patient is decreased.

20. The method of Claim 19, wherein the oxidative condition comprises bubbling a gaseous mixture of medical grade oxygen and ozone through the blood, for a period of from about 0.5 minutes to about 60 minutes.

21. The method of Claim 20, wherein the gaseous mixture has an ozone content of from about 0.1 to about 100 μg/mL.

22. The method of Claim 19, wherein the ultraviolet stressor is UV-C radiation.

23. The method of Claim 19, wherein the blood cells further are subjected extracorporeally to a heat stressor simultaneously with subjection to both an oxidative condition and an ultraviolet stressor.

24. The method of Claim 23, wherein the heat stressor is a temperature in the range of from about 40 to about 55°C.

25. The method of Claim 24, wherein the stressed mammalian blood cells comprise a volume of whole blood of from about 0.1 to about 400 mLs.

26. A method for the treatment or prophylaxis of chronic fatigue syndrome in a mammalian patient characterized by an excessive level of, or excessive sensitivity to, IL-6 cytokines in said patient, which method comprises:

selecting a patient suffering from or at risk of suffering from chronic fatigue syndrome;

withdrawing an aliquot of blood comprising blood cells from said patient;

subjecting said blood cells extracorporeally to stress comprising both oxidative conditions and ultraviolet conditions simultaneously;

administering to said patient an effective amount of stressed mammalian blood cells, wherein the level of IL-6 cytokines in said patient is reduced.

27. The method of Claim 26, wherein the stressed mammalian blood cells have additionally been extracorporeally subjected to heat stress simultaneously with subjection to both oxidative conditions and ultraviolet radiation.

28. The method of Claim 26, wherein the oxidative conditions comprise bubbling a gaseous mixture of medical grade oxygen and ozone through the blood, for a period of from about 0.5 minutes to about 60 minutes.

29. The method of Claim 28, wherein the gaseous mixture has an ozone content of from about 0.1 to about 100 μg/mL.

30. The method of Claim 26, wherein the ultraviolet stressor is UV-C radiation.

31. The method of Claim 27, wherein the heat stressor is a temperature in the range of from about 40 to about 55°C.

32. The method of Claim 31, wherein the stressed mammalian blood cells comprise a volume of whole blood of from about 0.1 to about 400 mLs.

EVIDENCE APPENDIX

No evidence submitted under §§1.130, 1.131, or 1.132 is relied upon by Appellant.

RELATED PROCEEDINGS APPENDIX

Appellant is unaware of any prior or pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the decision in this application.